Organic Chemistry
Current Research

Waszkielewicz, Organic Chem Curr Res 2014, 3:2
DOI: 10.4172/2161-0401.1000e135

Editorial Open Access

Short Commentary on Current Trends in Medicinal Chemistry of the Central Nervous System

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The incidence of central nervous system diseases is increasing due to elongation of lifetime of humans. It is related with injuries, neurodegenerative diseases, intoxication, as well as natural processes associated with ageing.

As a result, medicinal chemistry, which has emerged from organic chemistry, has undergone multiple trends and – depending on the indications – with various results. Many diseases have been eradicated, resulting in better quality of life and its elongation (e.g. analgesic, nontropic drugs). Other indications have arose and became unmet medical needs (e.g. neuropathic pain). Moreover, there are diseases which were poorly addressed fifty years ago and are still today (e.g. epilepsy, major depressive disorder).

Molecular modeling has aided discovery of some new drugs, due to belief that only specific ligands towards subtypes of receptors may be safe enough. This process resulted in creation of compound libraries and development of big pharma programs related with search for a specific drug towards single conditions. However, this strategy is limited to indications where the target is well known and influence on the target is sufficient to treat the symptom. In the cases where the pathomechanism of the disease is not well known – *in vivo* models are used for activity screening of compounds. If a specific drug active in a single mechanism of action is not effective enough, polytherapy is used, questioning sometimes the rationale for specific target development.

Due to the above fact, the expression "dirty pharmacophore" which meant a drug binding to many receptors, has been more and more often replaced by "rich pharmacophore". However, the new challenge is to obtain the desired cocktail of bound receptors, and the expected *in vivo* outcome, bearing in mind the complexity of ADME-Tox processes.

Another approach contrary to molecular modeling is synthesis of analogs of used drugs, or synthesis of new compounds which possess structural elements observed in biologically active compounds. In such strategy, a typical expression is "drug-like look" of the structure, using intuitively the Lipinski rule of five, taking into account parameters such as lipophilicity, pK_a, as well as potential metabolism based on the knowledge of toxicity of old drugs or natural compounds.

New receptors described by biologists have been another starting point for new active compound design. This in turn implies doubt related with pharmacological activity, safety, long-term toxicity, addiction, as well as influence on progress of the disease. Finally, it must be taken into account that proof of hypothesis related with such ligand activity is visible in humans, over ten years of research performed on thousands of animals.

The final aspect to be mentioned is quantities of compounds needed for screening which influence the methods used for their synthesis. The more the target is defined, the more molecular modeling approach is used, and the quantities are relatively small (about 15 mg) leaving possibility for a complicated structure. In case of *in vivo* screening, usually quantities of about 500 mg may be needed – which leaves possibility only for relatively simple structures and effective methods of synthesis with yield above 50%. As a consequence, the term "click chemistry" has arisen as a necessary limitation of the cost of research and medicines themselves. New peptide drugs have answered many diseases, but the cost and complexity, as well as immunological response to them limit their use to the most justified cases. On the other hand, peptides found their use in cosmetics chemistry, where they are used topically.

As a summary, it seems that medicinal chemistry will constantly develop in terms of therapeutic areas, chemical structures, and methods of synthesis.

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Received March 01, 2014; **Accepted** March 04, 2014; **Published** March 11, 2014

Citation: Waszkielewicz AM (2014) Short Commentary on Current Trends in Medicinal Chemistry of the Central Nervous System. Organic Chem Curr Res 3: e135. doi:10.4172/2161-0401.1000e135